DOI:
10.1111/jgs.14883

Document Version
Peer reviewed version

Low Dose Aspirin Use and Cognitive Function in Older Age: a Systematic Review and Meta-Analysis

Nicola Veronese[1,2*^], MD, Brendon Stubbs[3,4,5^], PhD, Stefania Maggi[2], MD, Trevor Thompson[6], PhD, Patricia Schofield[3], MD, Christoph Muller [4,5], MD, Ping-Tao Tseng[7], MD, Pao-Yen Lin [8,9], MD André F. Carvalho [10], MD, Marco Solmi[1,11-12], MD

[^] *Joint first authors*

[1] Institute for Clinical Research and Education in Medicine (I.R.E.M.), Padova, Italy.

[2] Aging Section, Institute of Neurosciences, Italian Research Council, Padova, Italy.

[3] Faculty of Health, Social Care and Education, Anglia Ruskin University, Chelmsford, United Kingdom.

[4]South London and Maudsley NHS Foundation Trust, London SE5 8AZ, UK.

[5] Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London SE5 8AF, UK.

[6] Faculty of Education and Health, University of Greenwich, London SE9 2UG, UK

[7] Department of Psychiatry, Tsyr-Huey Mental Hospital, Kaohsiung Jen-Ai's Home, Taiwan

[8] Department of Psychiatry, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

[9]Institute for Translational Research in Biomedical Sciences, Kaohsiung Chang Gung Memorial Hospital

[10] Translational Psychiatry Research Group, Department of Clinical Medicine, Faculty of Medicine, Federal University of Ceara, Fortaleza, CE, Brazil.

[11]Local Health Unit 17, Mental Health Department, Italy.

[12]Department of Neuroscience, University of Padova, Padova, Italy.

Corresponding author:

Nicola Veronese, MD

Department of Medicine - DIMED, GeriatricsDivision, University of Padova, Padova, Italy

Via Giustiniani, 2 - 35128 Padova, Italy

Phone: +39 0498218492; Fax: +39 0498211218

Email: ilmannato@gmail.com

Alternate Corresponding Author:

Brendon Stubbs

brendon.stubbs@kcl.ac.uk

Funding source: none.

Running head: aspirin and dementia

Abstract word count: 262

Main text word count: 2811

ABSTRACT

OBJECTIVES: Low-dose aspirin is efficacious for the prevention of cardiovascular and cerebrovascular conditions, established risk factors for the onset of poor cognitive status and dementia. We investigated whether low-dose aspirin (i.e. a daily dosage <300 mg) can influence the onset of cognitive impairment/dementia in observational studies and improve cognitive tests scores in randomized controlled trials (RCTs) in participants without dementia.

DESIGN: Systematic review and meta-analysis.

SETTING: Observational and interventional studies.

PARTICIPANTS: Subjects initially with no dementia/cognitive impairment.

MEASUREMENTS: Odds ratios (ORs) and 95% confidence intervals (CIs), adjusted for the maximum number of covariates from each study were used to summarize data on the incidence of dementia/cognitive impairment. Standardized mean differences (SMDs) were used for cognitive test scores in RCTs.

RESULTS: Of 2,341 initial hits, 8 studies were eligible and provided data for 36,196 participants without dementia/cognitive impairment at baseline (mean age 66 years, 63 % female). After adjusting for a median of 3 potential confounders, over a median follow-up period of 6 years, the use of low-dose chronic aspirin was not associated with a significant reduction in the onset of dementia or cognitive impairment (5 studies, N=26,159; OR=0.82; 95% CI [0.55,1.22]; p=0.33; I^2=67%). In three RCTs (N=10,037; median follow-up=5 years), the use of low-dose aspirin was not associated with significant improvements in global cognition (SMD=0.005; 95% CI: [-0.04,0.05]; p=0.84; I^2=0%) in individuals without dementia. Adherence was lower in aspirin compared to controls and the incidence of adverse events was higher.

CONCLUSION: This review found no evidence that low-dose aspirin buffers against cognitive decline/ dementia or improves cognitive test scores in RCTs.

Key words: aspirin, dementia, cognitive impairment, meta-analysis.

INTRODUCTION

Low-dose aspirin is often used for the prevention of cardiovascular disease (CVD) due to its anti-thrombotic properties.[1,2] Aspirin has anti-inflammatory properties and inflammation plays a pivotal role in several diseases.[4] Preclinical models suggest that aspirin may decrease neuroinflammation and oxidative stress in the central nervous system (CNS).[5,6] These pleiotropic mechanisms of action of aspirin could aid in the prevention of cognitive decline or dementia.

Cardiovascular and cerebrovascular conditions are established risk factors for poor cognitive status and dementia.[7–9] The relationship between vascular disease and cognitive decline and dementia can explained by the atherosclerotic process leading to plaque development and reduced oxygen availability to the brain.[10] Dementia and cardio- and cerebrovascular diseases share several risk factors, particularly with diabetes-mellitus.[11,12]

There has been growing interest in the use of drugs of a similar nature to aspirin, such as nonsteroidal anti-inflammatory drugs (NSAIDs) for the prevention of dementia[14]. An increasing body of research is suggesting a potential role for aspirin in the prevention of poor cognitive status. Since dementia is irreversible, understanding if low-dose aspirin is useful for the prevention of cognitive decline and improvement of cognitive function of those without dementia is important. A Cochrane systematic review including one RCT (n=70) published 15 years ago demonstrated no benefit in aspirin preventing vascular-dementia.[13] Since that time, further evidence has become available and an updated comprehensive meta-analysis is required.

Given the aforementioned limitations in the literature, this paper had the following aims. 1) Investigate whether low-dose aspirin use is associated with the onset of dementia and poor cognitive status in

observational studies. 2) whether low-dose aspirin usage results in improved cognitive test scores in RCTs among people without cognitive impairment/dementia. We hypothesized that low-dose aspirin could have a favorable role on cognition.

METHODS

This systematic review adhered to the PRISMA [16] and MOOSE [17] statements, and followed an *a priori* defined, but unpublished protocol.

Data sources and literature search strategy

Two investigators (NV and MS) independently searched PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials and Clinicaltrials.gov without language restrictions, from database inception until September 1st, 2016. Observational studies and RCTs investigating the effect of oral low-dose aspirin on the incidence of dementia and/or test scores assessing cognitive function in people without dementia/cognitive impairment at baseline were included. In PubMed, the following search strategy was used: (Aspirin OR acetylsalicylic acid) AND (cognit*). Conference abstracts and reference lists of included articles were hand-searched to identify any potential additional relevant articles. Any inconsistencies were resolved by consensus.

Study selection

Inclusion criteria for this meta-analysis were: i) use of an RCT or longitudinal study design; ii) use of low-dose aspirin (i.e. a daily dosage<300 mg[18]); iii) reporting data on dementia diagnosed through validated criteria; iv) reporting data of cognitive tests of global (e.g. mini-mental state examination, MMSE[19]) or specific cognitive functions in adults without dementia or cognitive impairment.

Studies were excluded if: i) not conducted in humans; ii) used a non-placebo control group (active controls, in RCTs); iii) used dosages of aspirin with anti-inflammatory aims (i.e. with a dosage $\geq$300 mg/daily or for brief periods, i.e. less than one year); iv) a standardized mean difference (SMD) or odds ratio (OR) could not be computed from the available data. If we encountered studies that did not

provide sufficient data for the meta-analysis, we contacted the authors twice over a month period to request additional data.

Data extraction

Two investigators (NV and BS) extracted data from the articles in a standardized file and a third independent investigator (MS) validated data extraction. We extracted data about authors, year of publication, country, setting, demographics (i.e. sample size, mean age and percentage of women), follow-up duration, diagnostic criteria or tests used for the diagnosis of dementia and cognitive impairment, daily dosage of aspirin. In longitudinal studies, we extracted the number and type of covariates used in the multivariate analyses. Moreover, we extracted data by treated with low-dose aspirin and controls. If information was missing, first and/or corresponding authors of the original article were contacted at least two times in a month.

Outcomes

For longitudinal studies, the primary outcome was the incidence of dementia or cognitive impairment during follow-up in the longitudinal studies. Dementia was ascertained through validated criteria, whilst cognitive impairment was ascertained according to predefined cut-offs of standardized tests for assessing cognitive status (i.e. a MMSE score $\leq$ 24/30) [19].

For RCTs, changes between follow-up and baseline of tests assessing cognition (such as global cognition, verbal memory or fluency) were extracted for participants without dementia or cognitive impairment at baseline in the group taking aspirin and in the control group (placebo/no intervention).

Assessment of study quality

Two authors (NV, BS) assessed the quality of the studies using the Newcastle-Ottawa Scale (NOS) to evaluate longitudinal studies [20] and the Jadad's scale[21] for assessing the quality of the RCTs.

Data synthesis and statistical analysis

All analyses were performed using Comprehensive Meta-Analysis (CMA) 3 (http://www.meta-analysis.com).

In the primary analysis, we compared the data regarding the incidence of dementia and cognitive impairment in people using low-dose aspirin vs. no treatment using the ORs with their 95% confidence intervals (CIs), adjusted for the maximum number of covariates available for each study. In the co-primary analysis, we compared cognitive tests values between participants treated with low dose aspirin vs. controls (placebo or no intervention). We calculated the difference between the means of the treatment and control groups, using the changes between follow-up and baseline data for each group, through SMD with 95% CIs. In all the analyses, a random-effect model was applied. [22]

Heterogeneity across studies was assessed by the I^2 metric and Cochran's Q chi-square statistics with a value$\geq$50% for the first and $p < 0.05$ indicating the presence of a significant heterogeneity. [23]

Publication bias was assessed by visually inspecting funnel plots and the Begg-Mazumdar Kendall tau[24] and the Egger bias test.[25] To account for publication bias, we used the trim-and-fill method, to adjust for any potential unpublished (imputed) studies.[26]

For all analyses, $p<.05$ was considered statistically significant.

RESULTS

Search results

Altogether, the search yielded 2,341 non-duplicated articles. After excluding 2,325 articles based on title/abstract review, 16 articles were retrieved for full text review and eight studies (5 longitudinal[27–31] and 3 RCTs [32–34]) were included (**Supplementary Figure S1**). Overall eight studies were excluded since they included active controls (i.e. people taking another drug, n=3), investigated acute effects of aspirin on cognition (i.e. a daily dose over 300 mg used for analgesic aims, n=2), were reviews (n=1),a protocol (n=1) or reported data as linear regression estimates, thus not meta-analyzable (n=1).

Study and participants' characteristics

Full descriptive details of the included studies are reported in **Supplementary Tables S 1-2**.

This meta-analysis included 36,196 participants, of which 8,484 (23.4%) received low-dose aspirin. The mean age was 66 years and the participants were mainly women (63%). All the studies were conducted among community-dwellers and in Europe (6 studies) or USA (2 studies).

Longitudinal studies

The five longitudinal studies[27–31] included 26,159 community-dwelling participants with a mean age of 65.1 years, mainly women for a median follow-up period of 6 years. Three studies[27,29,30] investigated dementia as outcome, whilst the other two[28,31] considered cognitive impairment (**Supplementary Table S1**). The quality of the studies was sufficient (NOS mean 6, 6-7)..[20]

Among the 26,159 participants, 3035 (11.6%) used low-dose aspirin. The participants using low-dose aspirin at baseline were significantly older (78.1±5.3 vs. 75.9±6.4 years, $p<0.0001$), whilst no differences emerged regarding the percentage of women (64% vs. 69%, $p=0.15$).

RCTs

The three RCTs[32–34] (two versus placebo[32,34] and one[33] as add-on therapy) included 10,037 participants aged on average 66.8 years, mainly women (74%). The median follow-up period was 5 years (range: 3-9.6). One RCT[33] used the MMSE score as tool for cognitive status, whilst the other two[32,34] used several tests, as shown in **Supplementary Table S2**. The quality of the studies was good.[21]

Meta-analysis of longitudinal studies

After adjusting for a median of 3 potential confounders (range: 0-7), the use of low-dose aspirin was not associated with any significant reduction in the onset of dementia or cognitive impairment (5 studies; OR=0.82; 95%CI: 0.55-1.22; p=0.33; I^2=67%; **Figure 1**). Considering each study separately, only one study [29] with the largest cohort available (n=23,915 participants at baseline) reported a significant decreased risk of dementia at follow-up, taking in account also 4 potential confounders (**see Supplementary Table S2**). Even though the three studies using dementia as outcome[27,29,30] reported a lower OR, (0.59 (95%CI: 0.33-1.05; p=0.84; I^2=33%) than the other two which examined cognitive impairment[28,31] [OR=0.96 (95%CI: 0.62-1.51; p=0.66; I^2=59%)], the interaction of aspirin use by outcome was not significant (p=0.18). After removing one study[30] (a conference abstract) the results did not significantly change (OR=0.72; 95%CI: 0.47-1.10; p=0.14; I^2=70%), with the studies assessing dementia reporting an OR=0.59 (95%CI: 0.33-1.05; p=0.07; I^2=33%).

Meta-analysis of randomized controlled trials

As reported in **Figure 2**, the use of low-dose aspirin was not associated with any improvement in global cognitive tests in the three RCTs including 10,037 participants[32–34] (SMD=0.00; 95%CI: -0.04 to 0.05; p=0.84; I^2=0%). Publication bias was unlikely.

Two studies [32,34] reported information regarding verbal memory and executive function/fluency tests. Whilst no significant differences emerged in terms of verbal memory tests (SMD=-0.02; 95%CI: -0.06 to 0.03; p=0.42; I^2=0%), the use of low-dose aspirin was associated with a significant small improvement in executive function/fluency tests (SMD=0.06; 95%CI: 0.02 to 0.11; p=0.006; I^2=0%). This improvement was estimated to correspond to 2.6 years younger age, and a substantial 20% lower risk of cognitive decline compared to the use of placebo[34] in a single study.

Compliance and adverse effects

In the three RCTs included, a lower percentage of participants using low-dose aspirin completed the RCTs compared to controls (69.9 vs. 75.9%, chi-square test p-value=0.005).

Only two studies (one longitudinal [27] and one RCT [33]) reported information regarding side effects. The prevalence of gastrointestinal adverse events was ten times higher in people taking aspirin compared to controls (15.2% vs. 1.4%, p<0.0001). Whilst the RCT[33] did not report the type of gastrointestinal side effects, the longitudinal study[27] reported a similar incidence of gastric ulcers between those taking and not taking aspirin (p=0.17).

DISCUSSION

In this meta-analysis, we found that the use of low-dose aspirin did not appear to be associated with a lower incidence of dementia and cognitive impairment in observational studies. Across RCTs, we found no evidence of improvement in cognitive test scores among people who were free from dementia or cognitive impairment. However, people using low-dose aspirin experienced a higher frequency of side effects (particularly gastrointestinal), although this information is limited to data from two studies.

Several hypotheses might explain these findings. First, the average age of the participants was 65 years. Previous research has suggested that the pathological changes typical of dementia happen 20 years before the clinical symptoms present [35], therefore the use of low-dose aspirin at this age may be 'too little and/or too late'. Second, participants may have been taking low dose aspirin for the secondary prevention of CVD or related conditions. Thus, pre-existing comorbidities at baseline may have interfered with low dose aspirins potential cognitive beneficial effects and explain the null result. Finally, genetic factors could play a role in this lack of effect of low-dose aspirin. One study investigated if the role of the APOE gene altered the association between nonsteroidal anti-inflammatory drug (NSAID) use and dementia risk, and found reduced risk of AD only in NSAID users with an APOE epsilon 4 allele.[37] Specific research is needed to clarify this potential hypothesis. Other factors may have accounted for our result across RCTs which also need to be considered. First, the number of people lost during follow-up could have influenced our results. Moreover, some of the cognitive tests, such as the MMSE, suffer from important limitations, such as the over estimation of cognitive impairments in persons over age 60 and in those with lower educational status.[38] In our meta-analysis, we tried to overcome this issue by using all of the tests available that assessed cognition and subcomponents such as executive function/fluency tests which may be improved by aspirin use.

However, the very small effect size detected in the latter suggests that the clinical significance of these findings is probably limited.

Our findings are in partial agreement with two recent meta-analyses considering the use of other NSAIDs on cognitive outcomes. While the use of NSAIDs was associated with a 28% decrease in dementia onset in the longitudinal studies[14], the findings from the RCTs did not support these observational findings.[39] Taken together, it appears there is no consistent evidence that the use of NSAIDs may delay or prevent the onset of either dementia or cognitive impairment over time. However future, adequately powered real world investigations are required to better understand if aspirin and other NSAIDs can delay or prevent dementia. Based on our findings, we suggest that future RCTs including more men and younger people are probably needed. In this context, the ASPREE (ASPirin in Reducing Events in the Elderly) study, an ongoing trial including 19,000 healthy participants aged 65 years and above could be of importance for better understanding the possible role of aspirin in the prevention of dementia and mild cognitive impairment.[40] However, particular attention should also be given to adherence and any adverse events from such studies and low cost and lower risk alternatives such as physical activity[41,42] and nutrition interventions[43] should also be considered in this regard.

Although few studies provided evidence on adherence and adverse events, the limited available evidence suggests that lower adherence could in part be explained by a higher incidence of adverse events. Gastrointestinal side effects appear to be particularly troublesome. Some experts have suggested that aspirin may lead to an increase in gut permeability (i.e. 'leaky gut'), which may lead to the translocation of bacterial products (e.g. lipopolysaccharide-LPS), which may increase microglial activation and therefore neuroinflammation.[6,44,45] Bearing in mind the possible limitations of our work,

these results suggest not only a lack of evidence that aspirin could protect against cognitive decline/dementia, but that it may increase adverse gastrointestinal events.

The findings of our meta-analysis should be interpreted within its limitations. First, we only identified a limited number of the RCTs. Although these studies were of high quality, with a large sample size and long follow-up period, other studies are needed to have a definitive conclusion. Second, the observational studies did not use the propensity score in their analyses which is the best method for comparing a population taking a drug with another one without.[46] Moreover, the possibility of a selection bias in longitudinal studies and the fact that a consistent percentage of people not taking aspirin took other NSAIDs might create another important bias in our results. Moreover, one study included the overwhelming majority of participants and thus could have had a large influence on the overall result.[28] Another limitation is the high heterogeneity observed in the longitudinal studies and that no meta-regression analysis was possible due to the limited number of studies for each outcome.[47] Fourth, no study assessed the effect of low-dose aspirin in reducing dementia risk by APOE epsilon 4 status, which this could be a relevant factor in establishing a link between aspirin use and cognitive decline. It may be possible that only people with this mutation had a reduced risk of dementia when taking aspirin as shown by a large study analyzing the interaction between APOE epsilon 4 status and NSAIDs.[37] Fifth, conclusions on side effects of aspirin are based on only two studies. Finally, although we accounted for potential confounding factors when data were available by using adjusted effect estimates in our pooled analyses, it was not possible to consider other potentially important, unidentified confounders. For instance, people on low-dose aspirin are more likely to be at risk of, or with a history of CVDs than those not on aspirin, and the indications for aspirin may vary across countries, and these may be influential factors. Thus, future research should attempt to consider, where possible, the impact of such factors on the relationship between aspirin and cognitive outcomes.

The strengths of our work includes a comprehensive search of several databases, and the inclusion of the largest possible number of participants, the long follow-up of each study and that, to the best of our knowledge, this is the first systematic review and meta-analysis to consider this issue.

In conclusion, our preliminary meta-analysis suggests that low-dose aspirin does not decrease the risk of poor cognitive status (in terms of dementia or cognitive impairment) nor improve cognitive tests in randomized controlled trials. Moreover, adherence to aspirin may be lower compared to control conditions and adverse events may be more common. Future trials, considering dementia onset as outcome, are needed to disentangle if low-dose aspirin could be used to improve cognitive status, and to test the possibility that low-dose aspirin has beneficial effects when taken over a longer period and at an earlier age than the observed population did.

ACKNOWLEDGMENTS

We thank Dr Caroline Williams-Gray, John Van Geest Centre for Brain Repair, University of Cambridge, UK for giving us the data requested.

Funding source: None.

Conflict of Interest Checklist:

Elements of Financial/Personal Conflicts	***NV**		**BS**		**SM**		**TT**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Employment or Affiliation		**X**		**X**		**X**		**X**
Grants/Funds		**X**		**X**		**X**		**X**
Honoraria		**X**		**X**		**X**		**X**
Speaker Forum		**X**		**X**		**X**		**X**
Consultant		**X**		**X**		**X**		**X**
Stocks		**X**		**X**		**X**		**X**

Royalties		**X**		**X**		**X**		**X**
Expert Testimony		**X**		**X**		**X**		**X**
Board Member		**X**		**X**		**X**		**X**
Patents		**X**		**X**		**X**		**X**
Personal Relationship		**X**		**X**		**X**		**X**
Elements of Financial/Personal Conflicts	**PS**		**CM**		**PTT**		**PYL**	
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Employment or Affiliation		**X**		**X**		**X**		**X**
Grants/Funds		**X**		**X**		**X**		**X**
Honoraria		**X**		**X**		**X**		**X**
Speaker Forum		**X**		**X**		**X**		**X**

Consultant		**X**		**X**		**X**		**X**
Stocks		**X**		**X**		**X**		**X**
Royalties		**X**		**X**		**X**		**X**
Expert Testimony		**X**		**X**		**X**		**X**
Board Member		**X**		**X**		**X**		**X**
Patents		**X**		**X**		**X**		**X**
Personal Relationship		**X**		**X**		**X**		**X**
Elements of Financial/Personal Conflicts	**AFC**		**MS**					
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Employment or Affiliation		**X**		**X**				
Grants/Funds		**X**		**X**				
Honoraria		**X**		**X**				

Speaker Forum		**X**		**X**				
Consultant		**X**		**X**				
Stocks		**X**		**X**				
Royalties		**X**		**X**				
Expert Testimony		**X**		**X**				
Board Member		**X**		**X**				
Patents		**X**		**X**				
Personal Relationship		**X**		**X**				

Author Contributions: Study concept and design: Veronese, Stubbs, Maggi; analysis and interpretation of data: Veronese, Stubbs, Solmi. Preparation of manuscript: Thompson, Muller, Tseng, Lin. Critical revision of the manuscript: Carvalho, Schofield, Maggi.

Sponsor's Role: none.

REFERENCES

1. Bartolucci AA, Tendera M, Howard G. Meta-Analysis of Multiple Primary Prevention Trials of Cardiovascular Events Using Aspirin. *Am J Cardiol*. 2011;107(12):1796-1801. doi:10.1016/j.amjcard.2011.02.325.
2. Berger JS, Lala A, Krantz MJ, Baker GS, Hiatt WR. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: A meta-analysis of randomized trials. *Am Heart J*. 2011;162(1). doi:10.1016/j.ahj.2011.04.006.
3. Rothwell PM, Wilson M, Elwin C-E, et al. Long-term effect of aspirin on colorectal cancer incidence and mortality: 20-year follow-up of five randomised trials. *Lancet*. 2010;376(9754):1741-1750. doi:10.1016/S0140-6736(10)61543-7.
4. Soysal P, Stubbs B, Lucato P, et al. Inflammation And Frailty In The Elderly: A Systematic Review And Meta-analysis. *Ageing Res Rev*. 2016. doi:10.1016/j.arr.2016.08.006.
5. Wu Y, Zhai H, Wang Y, et al. Aspirin-triggered lipoxin A 4 attenuates lipopolysaccharide-induced intracellular ROS in BV2 microglia cells by inhibiting the function of NADPH oxidase. *Neurochem Res*. 2012;37(8):1690-1696. doi:10.1007/s11064-012-0776-3.
6. Wang Y-P, Wu Y, Li L-Y, et al. Aspirin-triggered lipoxin A4 attenuates LPS-induced pro-inflammatory responses by inhibiting activation of NF-κB and MAPKs in BV-2 microglial cells. *J Neuroinflammation*. 2011;8(1):95. doi:10.1186/1742-2094-8-95.
7. Tatemichi TK, Paik M, Bagiella E, et al. Risk of dementia after stroke in a hospitalized cohort: results of a longitudinal study. *Neurology*. 1994;44(10):1885-1891. doi:10.1212/WNL.44.10.1885.
8. Newman AB, Fitzpatrick AL, Lopez O, et al. Dementia and Alzheimer's disease incidence in relationship to cardiovascular disease in the cardiovascular health study cohort. *J Am Geriatr Soc*. 2005;53(7):1101-1107. doi:10.1111/j.1532-5415.2005.53360.x.

9. Harrison SL, Ding J, Tang EYH, et al. Cardiovascular disease risk models and longitudinal changes in cognition: A systematic review. *PLoS One*. 2014;9(12). doi:10.1371/journal.pone.0114431.

10. Trevisan C, Veronese N, Bolzetta F, et al. Low Hemoglobin Levels and the Onset of Cognitive Impairment in Older People: The PRO.V.A. Study. *Rejuvenation Res*. March 2016. doi:10.1089/rej.2015.1768.

11. Li L, Hölscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: A review. *Brain Res Rev*. 2007;56(2):384-402. doi:10.1016/j.brainresrev.2007.09.001.

12. Katon W, Pedersen HS, Ribe AR, et al. Effect of Depression and Diabetes Mellitus on the Risk for Dementia: A National Population-Based Cohort Study. *JAMA psychiatry*. 2015;98195:1-8. doi:10.1001/jamapsychiatry.2015.0082.

13. Williams PS, Rands G, Orrel M, Spector A. Aspirin for vascular dementia. *Cochrane database Syst Rev*. 2000;(4):CD001296. doi:10.1002/14651858.CD001296.

14. Wang J, Tan L, Wang H-F, et al. Anti-inflammatory drugs and risk of Alzheimer's disease: an updated systematic review and meta-analysis. *J Alzheimers Dis*. 2015;44(2):385-396. doi:10.3233/JAD-141506.

15. McAuliffe L, Brown D, Fetherstonhaugh D. Pain and dementia: An overview of the literature. *Int J Older People Nurs*. 2012;7(3):219-226. doi:10.1111/j.1748-3743.2012.00331.x.

16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med*. 2009;6(7):e1000100. doi:10.1371/journal.pmed.1000100.

17. Stroup DF, Berlin J a, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA*. 2000;283:2008-2012. doi:10.1001/jama.283.15.2008.

18. Lloyd J, Bochner F. Aspirin: how low is low dose? *Aust Prescr*. 1996;19(3):79-81. doi:10.18773/austprescr.1996.070.

19. Folstein M, Robins L, Helzer J. THe mini-mental state examination. *Arch Gen Psychiatry*. 1983;40(7):812. http://dx.doi.org/10.1001/archpsyc.1983.01790060110016.

20. Wells G, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. *(Available from URL http//www.ohri.ca/programs/clinical_epidemiology/oxford.asp)*. 2012:2012. doi:10.2307/632432.

21. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12. http://www.ncbi.nlm.nih.gov/pubmed/8721797. Accessed January 7, 2015.

22. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi:10.1016/0197-2456(86)90046-2.

23. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ Br Med J*. 2003;327(7414):557-560. doi:10.1136/bmj.327.7414.557.

24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101. doi:10.2307/2533446.

25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(September):629-634. doi:10.1136/bmj.316.7129.469.

26. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics*. 2000;56:455-463. doi:10.1111/j.0006-341x.2000.00455.x.

27. Kern S, Skoog I, Östling S, Kern J, Börjesson-hanson A. Does low-dose acetylsalicylic acid prevent cognitive decline in women with high cardiovascular risk ? A 5-year follow-up of a non-

demented population-based cohort of Swedish elderly women. 2012. doi:10.1136/bmjopen-2012-001288.

28. Kelley BJ, Mcclure LA, Unverzagt FW, Kleindorfer D, Howard G, Wadley VG. NIH Public Access. 2016;63(2):390-392. doi:10.1111/jgs.13271.Regular.

29. Nilsson SE, Johansson ÆB, Takkinen ÆS. Does aspirin protect against Alzheimer ' s dementia ? A study in a Swedish population-based sample aged ‡ 80 years. 2003:313-319. doi:10.1007/s00228-003-0618-y.

30. Williams-Gray C, Mason S, Foltinye T, Barker R. Williams Gray.pdf. 2014;24(S1):S553.

31. Jonker C, Comijs HC, Smit JH. Does aspirin or other NSAIDs reduce the risk of cognitive decline in elderly persons ? Results from a population-based study. 2003;24:583-588.

32. Price JF, Stewart MC, Deary IJ, et al. Low dose aspirin and cognitive function in middle aged to elderly adults : randomised controlled trial. 2006:1-8. doi:10.1136/bmj.a1198.

33. Group C. Aspirin in Alzheimer ' s disease (AD2000): a randomised open-label trial. :41-49. doi:10.1016/S1474-4422(07)70293-4.

34. Kang JH, Cook N, Manson J, Grodstein F. health study cognitive cohort. 2007;(April). doi:10.1136/bmj.39166.597836.BE.

35. Reiman EM, Quiroz YT, Fleisher AS, et al. Brain imaging and fluid biomarker analysis in young adults at genetic risk for autosomal dominant Alzheimer's disease in the presenilin 1 E280A kindred: A case-control study. *Lancet Neurol*. 2012;11(12):1048-1056. doi:10.1016/S1474-4422(12)70228-4.

36. Waldstein SR, Ph D, Wendell CR, et al. NIH Public Access. 2011;58(1):38-43. doi:10.1111/j.1532-5415.2009.02618.x.NSAIDs.

37. Szekely CA, Breitner JCS, Fitzpatrick AL, et al. NSAID use and dementia risk in the Cardiovascular Health Study: role of APOE and NSAID type. *Neurology*. 2008;70(1):17-24.

doi:10.1212/01.wnl.0000284596.95156.48.

38. Naugle RI, Kawczak K. Limitations of the Mini-Mental State Examination. *Cleve Clin J Med*. 1989;56(3):277-281.

39. Miguel-Alvarez M, Santos-Lozano A, Sanchis-Gomar F, et al. Non-steroidal anti-inflammatory drugs as a treatment for Alzheimer's disease: a systematic review and meta-analysis of treatment effect. *Drugs Aging*. 2015;32(2):139-147. doi:10.1007/s40266-015-0239-z.

40. ASPREE Investigator Group. Study design of ASPirin in Reducing Events in the Elderly (ASPREE): a randomized, controlled trial. *Contemp Clin Trials*. 2013;36(2):555-564. doi:10.1016/j.cct.2013.09.014.

41. Ahlskog JE, Geda YE, Graff-Radford NR, Petersen RC. Physical exercise as a preventive or disease-modifying treatment of dementia and brain aging. *Mayo Clin Proc*. 2011;86(9):876-884. doi:10.4065/mcp.2011.0252.

42. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA*. 2008;300(9):1027-1037. doi:10.1001/jama.300.9.1027.

43. Ngandu T, Lehtisalo J, Solomon A, et al. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. *Lancet*. 6AD;385(9984):2255-2263. doi:http://dx.doi.org/10.1016/S0140-6736(15)60461-5.

44. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: Interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol*. 2015;28(2):203-209.

45. Hollander D. Intestinal permeability, leaky gut, and intestinal disorders. *Curr Gastroenterol Rep*. 1999;1(5):410-416. doi:10.1007/s11894-999-0023-5.

46. Haukoos JS, Lewis RJ. The Propensity Score. *JAMA*. 2015;314(15):1637-1638.

445 doi:10.1001/jama.2015.13480.

446 47. Higgins JP, Green S. *Cochrane Handbook for Systematic Reviews of*. Vol Version 5.; 2008.

447 doi:10.1002/9780470712184.

LEGENDS

Figure 1. Effect of low-dose aspirin on the onset of dementia or cognitive impairment in longitudinal studies.

Figure 2. Effect of low-dose aspirin on global cognitive tests in randomized controlled trials.

Supplementary Figure S1. PRISMA flow-chart

Supplementary Table S1. Descriptive characteristics of the longitudinal studies included.

Supplementary Table S2. Descriptive characteristics of the randomized controlled trials included.